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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/945,459	12/09/97	MAKISHIMA	F 146.1275

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EXAMINER	
ROMEO, D	
ART UNIT	PAPER NUMBER
1647	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/945,459	Makishima et al.
Examiner	**Art Unit**
David Romeo	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *14 Jun 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *17-48* is/are pending in the application.

4a) Of the above, claim(s) *29-40 and 48* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *17-28 and 41-47* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *17-48* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The request filed on 04/18/2001 (Paper No. 23) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08945459 is acceptable and a CPA has been established. An action on the CPA follows.

2. The amendments filed 04/18/2001 (Paper No. 24) and 06/14/2001 (Paper No. 26) have been entered. Claims 17-48 are pending.

3. Applicant's election with traverse of group I, claims 17-28, 41-47, in Paper No. 26 is acknowledged. The traversal is on the ground(s) that how could there be three patentably distinct inventions in the fourth Office action. This is not found persuasive because 37 CFR 1.142, "Requirement for restriction", provides that "[i]f the distinctness and independence of the inventions be clear, such requirement will be made before any action on the merits; however, it may be made at any time before final action in the case, at the discretion of the examiner. See MPEP 802, "Basis for Practice in Statute and Rules". An application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). Groups I-III are distinct for the reasons given in the Office action mailed 05/24/2001 (Paper No. 25). Furthermore, separate classification (i.e., class and subclass) of

distinct inventions is sufficient to establish a *prima facie* case that the search and examination of the plural inventions imposes a serious burden upon the Examiner. See M.P.E.P. § 803. Such separate classification is set forth in the Office action mailed 05/24/2001 (Paper No. 25). Applicant has offered no evidence to rebut this showing.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 29-40, 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 26.

5. Claims 17-28, 41-47 are being examined.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 103

7. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10)[1] in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27).

Celeste teaches mature MP52 containing the amino acid sequence of Celeste's SEQ ID NO: 4 (column 3, lines 51-52). Amino acids #2 to #120 of Celeste's SEQ ID NO: 4 are identical to applicants' SEQ ID NO: 1. Celeste teaches that the first cysteine of the seven cysteine domain of MP52 is encoded by the codon beginning at nucleotide #899 of Celeste's SEQ ID NO: 3 (column 7, full paragraph 3). The codon beginning at nucleotide #899 of Celeste's SEQ ID NO: 3 encodes amino acid #19 of Celeste's SEQ ID NO: 4. Celeste teaches human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of Celeste's SEQ ID NO: 4 are expected to retain activity (column 7, full paragraph 3). Celeste teaches that the MP52 protein appears to begin at nucleotide 845 off Celeste's SEQ ID NO: 3 and continues through nucleotide 1204 of Celeste's SEQ ID NO: 3 (column 7, full paragraph 2). Celeste teaches that purified MP52 proteins may be produced by culturing a host cell transformed with a DNA sequence of Celeste's SEQ ID NO:3 from nucleotide 845 to 1204 (column 7, full

[1]References cited by the examiner are in an alphanumeric format, such as "a1", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

paragraph 3). Bacterial cells may also be suitable hosts (paragraph bridging columns 8-9) and the bacterially expressed MP52 can be isolated using techniques that are well known in the art (column 9, full paragraph 1). In expressing mature MP52 in a bacterial host, according to the teachings of Celeste, one would use a DNA molecule encoding MP52 with the N-terminal sequence Met-Ala-Pro-. Celeste is silent with respect to the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1.

Ben-Bassat teaches that in the case of Met-Ala-Pro-IL2, 60% of the bacterially expressed protein also lost the alanine residue, while no alanine removal was detected from the in vitro methionine aminopeptidase (MAP) reaction. Ben-Bassat suggest that another aminopeptidase(s) might be responsible for the removal of the alanine residue. See page 755, paragraph bridging columns 1-2. Ben-Bassat also suggest obtaining a homogeneous protein product without the N-terminal methionine; purified MAP could be used to "polish" the frayed amino terminal sequences (page 756, paragraph bridging columns 1-2).

Hirel teaches that the catalytic efficiency of MAP is insensitive to a Met-Pro- sequence, but that a variant with a Met-Ala-Pro- N-terminal sequence confirmed the inhibitory role of proline at position 3 (page 8250, column 2, full paragraph 4).

Georgiou teaches that the production of proteins that are identical to the natural product are highly desirable in the pharmaceutical industry, that the difference of a single amino acid

residue can be deleterious to a patient receiving the protein and complicates approval of the product by the FDA (page 1240, paragraph bridging columns 1-2).

Ben-Bassat, Hirel, and Georgiou do not teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to express mature MP52 in bacteria and to isolate the bacterially expressed protein therefrom, as taught by Celeste, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to express mature MP52 in bacteria because gene cloning and expression in bacteria would provide an abundant source of readily purified protein. In expressing mature MP52 in bacteria one of ordinary skill in the art would reasonably expect to obtain mature MP52 with the following N-terminal amino acid sequences, according to the teachings of Ben-Bassat and Hirel: Met-Ala-Pro, Ala-Pro, and Pro. The mature MP52 with a Pro at the N-terminus is identical to the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to "polish" the frayed amino terminal sequence by using purified MAP, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because mature MP52 with the N-terminal amino acid sequence Met-Ala-Pro is not identical to the natural product, the natural product is highly desirable in the pharmaceutical industry, and the difference of a single amino acid residue can be deleterious to a patient receiving the protein and complicates approval of the product by the FDA.

Following the teachings of Celeste in view of Ben-Bassat, Hirel, and Georgiou on would obtain a mature MP52 with the N-terminal amino acid sequences Ala-Pro, and Pro. Celeste in view of Ben-Bassat, Hirel, and Georgiou do not teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins.

Tonouchi teaches the removal of an N-terminal Ala with aminopeptidase P (Figure 3). The digestion was performed completely (page 33, paragraph bridging columns 1-2). The examiner has interpreted the term "performed completely" to indicate that the mature BSF-2 was without residual proteins.

Thompson at the paragraph bridging columns 1-2 teaches that it is generally considered desirable for clinical use to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule.

Tonouchi and Thompson do not teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a mature MP52 with the N-terminal amino acid sequences Ala-Pro, and Pro, as taught by Celeste in view of Ben-Bassat, Hirel, and Georgiou, and to modify that teaching by completely removing with aminopeptidase P the N-terminal Ala, as taught by Tonouchi, of the residual mature MP52 with the N-terminal amino acid sequence Ala-Pro, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because it is generally

considered desirable for clinical use to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule. Celeste in view of Ben-Bassat, Hirel, and Georgiou, and further in view of Tonouchi and Thompson teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins. The invention is prima facie obvious over the prior art.

8. Claims 17, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27) as applied to claim 17 above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10).

Celeste in view of Ben-Bassat, Hirel, and Georgiou, and further in view of Tonouchi and Thompson teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins. Celeste in view of Ben-Bassat, Hirel, and Georgiou, and further in view of Tonouchi and Thompson are silent with respect to said protein being a homodimer.

Hotten teaches that native GDF-5 is a dimer of the disulfide linked mature part of the protein as is seen in other TGF-β family members (page 650, first paragraph of discussion). GDF-5 is MP52. Cerletti teaches a process for the production of biologically active, dimeric, mature TGF-β-like proteins. The process comprises culturing an *E. coli* host that has been transformed with a plasmid containing DNA encoding the amino acid sequence of a mature TGF-

β-like protein (page 7, lines 9-14 and lines 40-41), solubilizing inclusion bodies obtained by culturing said *E. coli*, purifying the monomer protein from the solubilized solution, refolding the monomer protein into a dimer protein, and purifying same (page 7, line 56 through page 8, line 15).

Hotten and Cerletti do not teach the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins, as taught by Celeste in view of Ben-Bassat, Hirel, and Georgiou, and further in view of Tonouchi and Thompson, and to modify that teaching by forming native biologically active dimers, as taught by Hotten and Cerletti, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to form the native, biologically active form of the protein. The invention is prima facie obvious over the prior art.

9. Claims 17-28, 41-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27) as applied to claim 17 above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10) as applied to claim 18 above and further in view of Neidhardt (1, cited by Applicants).

Celeste in view of Ben-Bassat, Hirel, and Georgiou, and further in view of Tonouchi and Thompson teach native biologically active dimers of the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins.

Neidhardt teaches a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects (page 9, full paragraph 1), and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising an amount of a native biologically active dimer of a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins effective for the healing of bone and/or cartilage with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to make a composition suitable for the healing of bone and/or cartilage. The examiner has interpreted an amount effective to heal bone and/or cartilage as an amount effective to treat the recited cartilage and/or bone diseases.

In addition, Celeste teaches "[t]he compositions of the invention may comprise, in addition to a tendon/ligament-inducing protein such as BMP-12 or VL-1 (BMP-13), other therapeutically useful agents including MP52, epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and fibroblast growth factor-4 (FGF-4), parathyroid hormone (PTH), leukemia inhibitory factor (LIF/HILDA/DIA), insulin-like growth factors (IGF-I and IGF-II). Portions of these agents may

also be used in compositions of the present invention. For example, a composition comprising both BMP-2 and BMP-12 implanted together gives rise to both bone and tendon/ligament-like tissue. Such a composition may be useful for treating defects of the embryonic joint where tendon, ligaments, and bone form simultaneously at contiguous anatomical locations, and may be useful for regenerating tissue at the site of tendon attachment to bone. It is contemplated that the compositions of the invention may also be used in wound healing, such as skin healing and related tissue repair. The types of wounds include, but are not limited to burns, incisions and ulcers. (See, e.g. PCT Publication WO84/01106 for discussion of wound healing and related tissue repair). It is expected that the proteins of the invention may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one protein of the invention with a therapeutic amount of at least one of the BMP proteins described above. Such compositions may comprise separate molecules of the BMP proteins or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-12 related protein subunit and a subunit from one of the "BMP" proteins described above. Thus, the present invention includes compositions comprising a purified BMP-12 related polypeptide which is a heterodimer wherein one subunit comprises the amino acid sequence from amino acid #1 to amino acid #104 of SEQ ID NO:2, and one subunit comprises an amino acid sequence for a bone morphogenetic protein selected from the group

consisting of BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10 and BMP-11. A further embodiment may comprise a heterodimer of disulfide bonded tendon/ligament-like tissue inducing moieties such as BMP-12, VL-1 (BMP-13) or MP52. For example the heterodimer may comprise one subunit comprising an amino acid sequence from #1 to #104 of SEQ ID NO:2 and the other subunit may comprise an amino acid sequence from #1 to #120 of SEQ ID NO:4 or #1 to #120 of SEQ ID NO:26. Further, compositions of the present invention may be combined with other agents beneficial to the treatment of the defect, wound, or tissue in question. The preparation and formulation of such physiologically acceptable protein compositions, having due regard to pH, isotonicity, stability and the like, is within the skill of the art. The therapeutic compositions are also presently valuable for veterinary applications due to the lack of species specificity in TGF-β proteins. Particularly domestic animals and thoroughbred horses in addition to humans are desired patients for such treatment with the compositions of the present invention. The therapeutic method includes administering the composition topically, systemically, or locally as an injectable and/or implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pryogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than the proteins which may also optionally be included in the composition as described above, may alternatively or additionally, be

administered simultaneously or sequentially with the composition in the methods of the invention. In addition, the compositions of the present invention may be used in conjunction with presently available treatments for tendon/ligament injuries, such as suture (e.g., vicryl sutures or surgical gut sutures, Ethicon Inc., Somerville, N.J.) or tendon/ligament allograft or autograft, in order to enhance or accelerate the healing potential of the suture or graft. For example, the suture, allograft or autograft may be soaked in the compositions of the present invention prior to implantation. It may also be possible to incorporate the protein or composition of the invention onto suture materials, for example, by freeze-drying. The compositions may include an appropriate matrix and/or sequestering agent as a carrier. For instance, the matrix may support the composition or provide a surface for tendon/ligament-like tissue formation and/or other tissue formation. The matrix may provide slow release of the protein and/or the appropriate environment for presentation thereof. The sequestering agent may be a substance which aids in ease of administration through injection or other means, or may slow the migration of protein from the site of application. The choice of a carrier material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined. Preferred matrices include collagen-based materials, including sponges, such as

Helistat.RTM. (Integra LifeSciences, Plainsboro, N.J.), or collagen in an injectable form, as well as sequestering agents, which may be biodegradable, for example hyalouronic acid derived. Biodegradable materials, such as cellulose films, or surgical meshes, may also serve as matrices. Such materials could be sutured into an injury site, or wrapped around the tendon/ligament.

Another preferred class of carrier are polymeric matrices, including polymers of poly(lactic acid), poly(glycolic acid) and copolymers of lactic acid and gycolic acid. These matrices may be in the form of a sponge, or in the form of porous particles, and may also include a sequestering agent. Suitable polymer matrices are described, for example, in WO93/00050, the disclosure of which is incorporated herein by reference. Preferred families of sequestering agents include blood, fibrin clot and/or cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The mount of sequestering agent useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the activity of the progenitor cells.

Additional optional components useful in the practice of the subject application include, e.g. cryogenic protectors such as mannitol, sucrose, lactose, glucose, or glycine (to protect the protein from degradation during lyophilization), antimicrobial preservatives such as methyl and propyl parabens and benzyl alcohol; antioxidants such as EDTA, citrate and BHT (butylated hydroxytoluene); and surfactants such as poly(sorbates) and poly(oxyethylenes); etc."

See paragraph bridging columns 11-12 through paragraph bridging columns 13-14.

The specification at page 7, lines 12-18, teaches that injectable powders are lyophilized preparations, and Celeste at paragraph bridging columns 13-14 teaches the lyophilization of pharmaceutical compositions comprising MP52 and a pharmaceutically acceptable carrier.

With respect to claims 45, 46 the limitation "for cartilage or bone grafting using natural or artificial bone" has been interpreted as an intended use of the claimed pharmaceutical composition.

10. Applicants argue that it was extremely difficult to isolate mature MP52. Applicants' arguments have been fully considered but they are not persuasive. The prior provides the requisite motivation to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule. Following the procedures of the cited prior art, it would only be necessary to treat the heterogeneous material with aminopeptidases in order to obtain the homogeneous material.

Applicants' arguments regarding the expression of MP52 in eukaryotes do not appear to be germane to the instant rejection because; the claims are not limited to the expression of MP52 in eukaryotes; the cited references pertain the bacterial expression of MP52; although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims; and, expression of MP52 in eukaryotes is a process limitation and is not viewed as positively limiting the claimed MP52, as it is assumed that equivalent products are obtainable by multiple routes.

Applicants' arguments with respect to Hirel have been considered but they are not persuasive because Hirel at page 8250, right column, teaches that in the case of a variant with a Met-Ala-Pro N-terminal sequence excision dropped to 62%, thereby motivating one of ordinary skill in the art to use the procedures in the cited prior art to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule. Although Applicants' process of producing mature MP52 may be novel or unobvious, the claims are not limited to a novel or unobvious process.

Contrary to Applicants' assertions the examiner cannot find an instance wherein Celeste "contends that MP52 does not show any cartilage/bone-inducing activity". Furthermore, Neidhardt (1, cited by Applicants) teaches a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects and discloses the administration of such a composition to humans (page 9, full paragraph 1). There is

no evidence of record that the shortened form of MP52 would have been expected to have a reduced biological activity. Furthermore, obviousness does not require absolute predictability, only a reasonable expectation of success, i.e., a reasonable expectation of obtaining similar properties. Celeste is evidence that there was a reasonable expectation of success. See "the DNA sequence from nucleotides #845, #893 or #899 to #1201 or #1204 are expected to encode active proteins" at column 7, lines 57-59.

Claim Objections

11. Claim 20 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

12. Claims 17-28, 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. For the purposes of this rejection claim 17 is interpreted as being directed to a protein consisting of the amino acid sequence of SEQ ID NO: 1, free of proteins comprising the amino acid sequence of SEQ ID NO: 1 with an Ala or Met-Ala at the N-

terminus of SEQ ID NO: 1. Support for the limitation "without residual proteins consisting of the amino acid sequence as shown in SEQ ID NO: 1, the said protein with an additional Ala (120 amino acids) and the said protein with Met and Ala (121 amino acids) at the N-terminus" cannot be found in the specification or claims as originally filed and the introduction of such a limitation raises the issue of new matter.

13. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 17 recites the limitation "said protein with an additional Ala". The antecedent basis for this limitation is unclear because there are two earlier recitations of protein, i.e. "isolated protein" and "residual proteins", and it is unclear which is intended. Claim 17 recites the limitation "said protein with Met and Ala". The antecedent basis for this limitation is unclear because there are three earlier recitations of protein, i.e. "isolated protein", "residual proteins", and "said protein with an additional Ala", and it is unclear which is intended. In the event that the antecedent basis for the limitations "said protein with an additional Ala" and "said protein with Met and Ala" is intended to be "residual proteins", then there is insufficient antecedent basis for these limitations in the claims because the term "residual proteins" is plural and the limitations are singular.

b. Claims 45, 46 are indefinite over the recitation of "for cartilage or bone grafting using natural or artificial bone" because it is unclear if the limitation is an intended use or if it is intended to be a material limitation to the components of the pharmaceutical composition. The metes and bounds of the claim(s) are not clearly set forth. If the limitation is intended to be a material limitation it is suggested that the claims recite a pharmaceutical composition comprising natural or artificial bone.

Conclusion

14. No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

JUNE 27, 2001